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Abstract: Striatal abnormalities play a crucial role in the pathophysiology of schizophrenia. Growing evidence suggests an association between aberrant striatal activity during reward anticipation and symptom dimensions in schizophrenia. However, it is not clear whether this holds across the psychosis continuum. The aim of the present study was to investigate alterations of ventral striatal activation during reward anticipation and its relationship to symptom expression in persons with schizotypal personality traits (SPT) and first-episode psychosis. Twenty-six individuals with high SPT, 26 patients with non-affective first-episode psychosis (including 13 with brief psychotic disorder (FEP-BPD) and 13 with first-episode schizophrenia [FEP-SZ]) and 25 healthy controls underwent event-related functional magnetic resonance imaging while performing a variant of the Monetary Incentive Delay task. Ventral striatal activation was positively correlated with total symptom severity, in particular with levels of positive symptoms. This association was observed across the psychosis continuum and within each subgroup. Patients with FEP-SZ showed the strongest elevation of striatal activation during reward anticipation, although symptom levels did not differ between groups in the psychosis continuum. While our results provide evidence that variance in striatal activation is mainly explained by dimensional symptom expression, patients with schizophrenia show an additional dysregulation of striatal activation. Trans-diagnostic approaches are promising in order to disentangle dimensional and categorical neural mechanisms in the psychosis continuum.

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Ventral Striatal Dysfunction and Symptom Expression in Individuals With Schizotypal Personality Traits and Early Psychosis

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Striatal abnormalities play a crucial role in the pathophysiology of schizophrenia. Growing evidence suggests an association between aberrant striatal activity during reward anticipation and symptom dimensions in schizophrenia. However, it is not clear whether this holds across the psychosis continuum. The aim of the present study was to investigate alterations of ventral striatal activation during reward anticipation and its relationship to symptom expression in persons with schizotypal personality traits (SPT) and first-episode psychosis. Twenty-six individuals with high SPT, 26 patients with non-affective first-episode psychosis (including 13 with brief psychotic disorder (FEP-BPD) and 13 with first-episode schizophrenia [FEP-SZ]) and 25 healthy controls underwent event-related functional magnetic resonance imaging while performing a variant of the Monetary Incentive Delay task. Ventral striatal activation was positively correlated with total symptom severity, in particular with levels of positive symptoms. This association was observed across the psychosis continuum and within each subgroup. Patients with FEP-SZ showed the strongest elevation of striatal activation during reward anticipation, although symptom levels did not differ between groups in the psychosis continuum. While our results provide evidence that variance in striatal activation is mainly explained by dimensional symptom expression, patients with schizophrenia show an additional dysregulation of striatal activation. Trans-diagnostic approaches are promising in order to disentangle dimensional and categorical neural mechanisms in the psychosis continuum.

Key words: neuroimaging/reward processing/schizophrenia/positive symptoms/negative symptoms/psychosis continuum

Introduction

Neuroimaging studies have provided increasing evidence for striatal abnormalities as a core deficit in the pathophysiology of schizophrenia.[1–6] In this context, functional magnetic resonance imaging (fMRI) research has suggested that the blood-oxygen-level dependent (BOLD) signal during reward anticipation could serve as a marker to investigate striatal dysfunctions in patients.[7–9]

While a picture of striatal dysfunction and its association with symptoms begins to emerge for patients with chronic schizophrenia, it is not clear whether this extends across a continuum of psychosis (figure 1A). In a psychosis continuum concept, schizotypy and early psychosis can be described as at-risk stages for the development of chronic schizophrenia, the extreme end of the continuum.[10–12] Furthermore, psychotic-like symptoms and schizotypal traits in healthy individuals contribute to social disabilities even on a subclinical level.[12–14] However, neuroimaging studies investigating striatal activation during reward anticipation across a broad spectrum of psychosis remain sparse and inconclusive. Compared to healthy controls (HCs), differences in ventral striatal activity were observed in studies in patients with first-episode schizophrenia (FEP-SZ) and first-degree relatives of patients with schizophrenia.[15–18] Other studies including patients with broadly defined first-episode psychosis (not restricted to schizophrenia and schizophreniform disorder) or individuals at-risk for psychosis did not report any group differences, but focused more on the relationship with symptom expression.[19–23] This work supports the idea that on a group level reduced activation of the striatum may be more strongly related to schizophrenia or chronic forms of psychosis than to psychotic disorders in general. Importantly, these divergent findings highlight the importance of using dimensional approaches to investigate the neural basis of psychosis rather than restricting research to group differences.

In this context, one important line of research aims to elucidate how striatal dysfunction contributes to

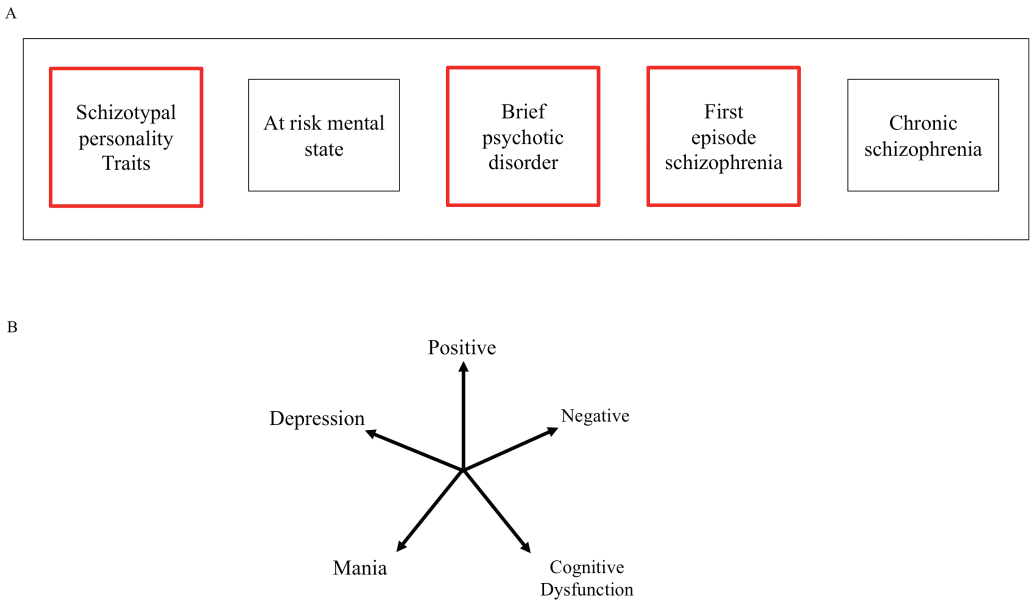

Fig. 1. Symptom dimensions in the psychosis continuum. (A) Simplified model of the psychosis continuum and its putative separation into subgroups. Subgroups investigated in the present study are outlined with a red rectangle. (B) Symptom dimensions in psychosis adapted from Kapur and van Os.[71]

symptom dimensions in psychosis (figure 1B).[9] Again, the most consistent evidence comes from studies in schizophrenia reporting an association between negative symptoms and blunted striatal activity during reward anticipation mainly in chronic medicated patients.[24–27] In addition, this association has also been observed in first-degree relatives of patients with schizophrenia.[18] Concerning positive symptoms, the literature strongly suggests an association with diminished striatal activity to relevant stimuli in unmedicated first-episode psychosis patients and individuals at ultra-high risk, which is consistent with the aberrant salience model of psychosis.[15,21] However, on a meta-analytic level including studies with unmedicated and medicated patients the association of neural alterations during reward processing and positive symptoms is less clearly delineated.[24] Furthermore, the association between striatal dysfunction and depressive symptoms is well described within depressive disorders[28,29] but data are limited for schizophrenia.[30,31] Most research did not take into account the neural basis of symptom dimensions on a psychosis continuum with broadly defined first-episode psychosis patients or individuals with schizotypal personality traits (SPT). Only recently, researchers have begun to shed light on this important question, but data are still very limited.[22,32–34] Importantly, with respect to individuals with schizotypal traits no study has ever investigated reward anticipation to identify neural correlates of symptom expression.

Therefore, the aim of the present study was 3-fold: (1) to investigate striatal activation during reward anticipation in individuals with SPT and a broad spectrum of patients with first-episode psychosis including patients with schizophrenia and patients with brief psychotic disorder, (2) to investigate neural correlates of negative and positive symptoms across the psychosis continuum, and (3) to identify categorical group differences between the 3 subgroups in the psychosis continuum. Based on previous studies discussed above,[19,21,23,25,35] we expected symptom expression but not group membership to be associated with aberrant ventral striatal activity during reward anticipation.

Methods

Participants

Initially, 27 patients with first-episode non-affective psychosis (FEP), 27 healthy individuals with high SPT, and 26 HC participants were included. Three participants (1 FEP, 1 SPT, 1 HC) were excluded because of head movement during fMRI scanning.

Individuals with FEP were recruited during their first psychiatric admission in outpatient ($n = 6$) and inpatient ($n = 20$) units of the Psychiatric Hospital of the University of Zurich. All FEP patients received a stable dose of atypical antipsychotics. Inclusion criterion was a clinical diagnosis of brief psychotic disorder, schizophreniform disorder or schizophrenia confirmed in a structured Mini-International Neuropsychiatric Interview for DSM-IV (MINI).[36] We excluded participants with any other current DSM-IV axis I disorder (in particular current substance use disorder and substance-induced psychotic disorder), lorazepam more than 1 mg/d, florid psychotic symptoms, ie, any positive subscale item score 5 or higher as measured with the Positive and Negative Syndrome Scale (PANSS),[37] or extrapyramidal side

effects.[38] Regarding inclusion criteria, it has to be noted that patients took part in a larger study protocol and therefore patients with higher psychotic symptom levels had to be excluded to ensure adequate task performance. Comorbid lifetime diagnoses of individuals with FEP are provided in supplementary table S1.

Individuals with schizotypal traits were recruited using an online form of the Schizotypal Personality Questionnaire (SPQ).[39] 956 participants completed the questionnaire (mean score 16.66 [SD 11.34]). Individuals with the highest SPQ total scores (upper 10% of the SPQ total score) were invited to participate in the study. Exclusion criteria were any current or past Axis I disorder confirmed with the MINI,[36] as well as use of psychopharmacological drugs. For further details on SPT participants and inclusion criteria of HCs see supplementary methods. The local ethics committee of the Canton Zurich approved the study, and all participants gave written informed consent.

Psychopathological Assessment

All FEP patients and SPT individuals underwent a detailed psychopathological assessment. Severity of positive and negative symptoms was assessed with the PANSS. In order to assess psychosis dimensions, we used a 5-factor model of the PANSS in our subsequent analysis.[40] To thoroughly assess negative symptoms with regard to the 2 symptom dimensions of apathy (deficits in motivation and pleasure) and diminished expression (blunted affect, alogia), we applied the previously used German version of the Brief Negative Symptom Scale (BNSS).[25,41–43] Additionally, we used the Calgary Depression Scale for Schizophrenia (CDSS)[44] to identify depressive symptoms. For details on clinical and neuropsychological assessment see supplementary methods.

fMRI Task

We used a variant of the Monetary Incentive Delay (MID) Task with stimuli based on the Cued-Reinforcement-Reaction-Time Task (figure 2), which was originally developed by Simon et al.[25,45,46,47] In contrast to the original MID Task, we employed a task design, in which reward was directly determined by the behavior (response time) of participants (supplementary figure S1). This adaptation allowed us to investigate the motivational properties of reward anticipation in the presence of action-outcome contingencies. Before starting the experiment, we informed all participants that they would receive the accumulated amount of money they won during the 2 experimental sessions. The maximum amount of money to be won was 50 Swiss Franc (1 CHF = 1.08 US$). We calculated the amount of money to be won for each trial on the basis of the response times of the previous 15 individual trials (supplementary figure S1). This approach was used in order to account for individual differences in response time and thus ensure constant and similarly high rewards in all groups. Excluding 2 training sessions, the experiment contained 2 runs with 36 trials of about 10 seconds each. The inter-trial interval was

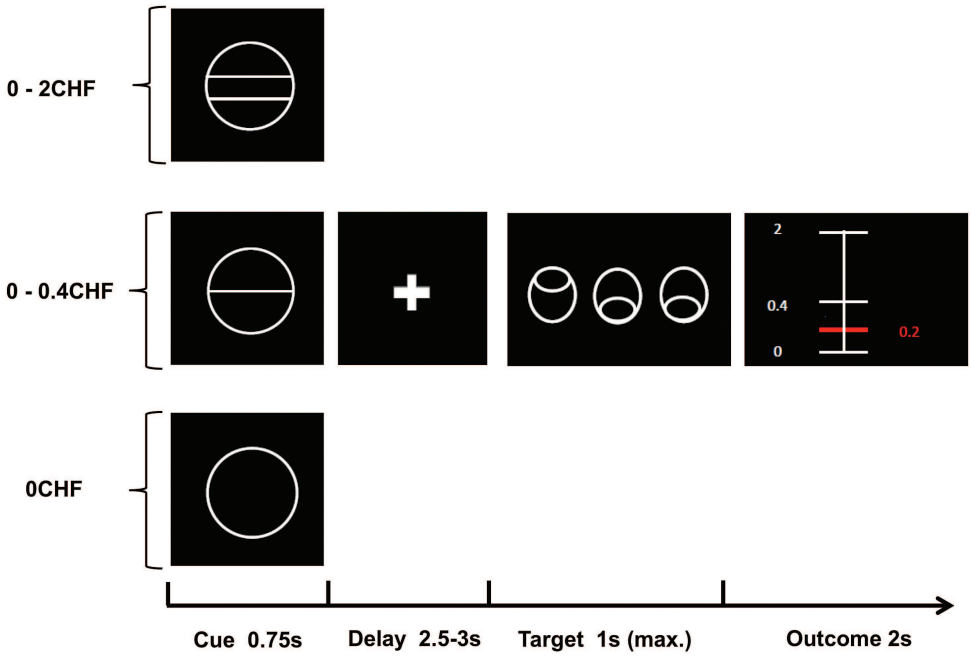

Fig. 2. At the beginning of each trial, 1 of 3 different cues was presented for 0.75 second. The cue indicated the maximum possible amount participants could gain in that trial, ie, high-reward condition 0 to 2 Swiss Francs (CHF), low-reward condition 0 to 0.40 CHF, or neutral condition 0 CHF (1 CHF = 1.08 US$). After a delay the participants had to identify an outlier from 3 presented circles and press a button as fast as possible. Immediately after the button press, participants were notified about the money won.

jittered from 1 second to 9 seconds with a mean of 3.5 seconds. In total, 1 run lasted about 6 minutes.

Behavioral Data Analysis

We performed a 2-way repeated measures ANOVA to investigate response time, the main behavioral outcome measure in the present study. Group was defined as between-subject factor and the different reward conditions (neutral, low, high) as within-subject factor. We further calculated reward-related speeding, by subtracting the response time during the neutral condition (CHF 0) from the response time during the high-reward condition (CHF 2.0), which was then divided by the mean of these 2 conditions.

Image Acquisition and Analyses

For acquisition parameters and image preprocessing see supplementary methods. On the first level this event-related design was analyzed with a general linear model (GLM) approach. Three separate regressors were modeled for the anticipation phases: anticipation of no reward (CHF 0), anticipation of low reward (CHF 0–0.40) and anticipation of high reward (CHF 0–2.0). For the outcome phases we included 1 regressor for each condition (3 basic regressors) and 2 parametrically modulated regressors corresponding to the obtained reward amount, 1 for the low and 1 for the high-reward condition. Additionally, target presentation (1 regressor) and error trials (3 regressors) were modeled as regressors of no interest. In total, the first level model included 12 regressors. We used the canonical hemodynamic response function for convolving all explanatory variables. To analyze reward anticipation, we calculated the reward anticipation contrast high-reward anticipation (CHF 2.0) vs no-reward anticipation (CHF 0). At the second level of analysis, we included the resulting individual contrast images of all participants in a random-effects model. We assessed within-group activation using 1 sample t tests and between-group activation using 2 sample t tests. Our main focus was a region of interest analysis of reward anticipation in the ventral striatum (VS).

Region of Interest Analysis

In line with our a priori hypothesis, we defined the VS as region of interest (ROI). Coordinates for the VS were derived from a meta-analysis of Knutson and colleagues (left: $x = -12$, $y = 10$, $z = -2$; right: $x = 10$, $y = 8$, $z = 0$, both 9 mm spheres including 389 voxels),[48] which has been used in previous studies in patients with bipolar disorder and schizophrenia.[25,49] The mean contrast signal for the contrast anticipation of high reward vs no reward was extracted and averaged across all voxels in the VS ROI using the REX toolbox (http://web.mit.edu/swg/software.htm).

Statistical Analysis

To identify group differences we performed 1-way ANCOVAs with VS activation estimate as dependent variable and age and cognition as covariates.

We tested our main hypothesis by calculating Spearman correlation (r_s) at the psychopathological and neural level dimensionally across SPT participants and FEP patients. Concerning psychopathology, we investigated associations between the symptom dimensions of negative symptoms (BNSS apathy factor and BNSS diminished expression factor), positive symptoms (PANSS positive factor) and depressive symptoms (CDS total score). At the neural level we investigated the association of symptom dimensions with the mean contrast signal in the VS. Partial correlations were calculated to identify potential confounding variables. To account for the use of 2 separate VS ROIs (right and left VS), Bonferroni correction for multiple comparisons was applied for the main analyses.

Results

Demographic and Clinical Data

Demographic and clinical data area are summarized in table 1.

Behavioral Data: Reward Decreases Response Time Across Groups

Response times showed a significant main effect of reward ($F(2, 132) = 104.29$, $P < .001$), but no significant effect of group ($F(2, 74) = 1.22$, $P = .30$) or group × reward interaction ($F(2, 132) = 0.97$, $P = .42$). Bonferroni post hoc pairwise comparison of response times revealed significant differences between all reward conditions (all Ps $< .001$). These results indicate intact reward-related speeding in all groups. Accordingly, we did not observe any significant group differences in reward-related speeding ($F(2, 74) = 0.818$, $P = .44$), error rates ($\chi^2(2) = 2.34$, $P = .32$), and total gain ($F(2, 74) = 1.65$, $P = .20$).

Psychopathological Data—Group Comparisons

We found that apathy ($U = 208.5$, $P = .02$) was significantly higher and global functioning ($U = 199.5$, $P = .02$) significantly lower in the FEP than in the SPT group (table 1). In all other psychopathological measures we did not observe any significant group differences between FEP and SPT participants (table 1).

Psychopathological Data—Apathy is Associated With Positive Symptoms and Depression

Across FEP and SPT participants, we found a significant association of apathy with positive symptoms ($r_s = .31$, $P = .02$) and depressive symptoms ($r_s = .44$, $P = .001$). This symptom overlap suggests that apathy may have

Table 1. Demographic, Psychopathological, and Clinical Data

	HCs (n = 25)	SPT Participants (n = 26)	FEP Patients (n = 26)	Test Statistic (U/F/χ^2)
Age	28.8 (6.7)	29.5 (10.3)	24.1 (6.9)	χ^2 = 8.08*
Gender (f, m)	6f, 19m	9f, 17m	5f, 21m	χ^2 = 1.67
Education, y	13.9 (2.4)	15.3 (2.6)	12.1 (2.5)	χ^2 = 16.7***
Duration of illness, mo			5.4 (6.2)	
Duration of antipsychotic treatment in days		41 (30)		
Diagnosis[a]			SZ = 13; BPD = 13	
Chlorpromazine equivalents (mg/d)			268.8 (244.5)	
BNSS apathy[b]		8.4 (8.3)	13.6 (8.0)	U = 208.5*
BNSS diminished expression[c]		3.1 (4.5)	6.0 (6.5)	U = 248.0
BNSS total		11.9 (8.3)	20.0 (11.9)	U = 200.0*
PANSS positive factor[d]		5.4 (2.4)	5.9 (1.7)	U = 257.5
PANSS total		40.9 (8.7)	44.5 (10.6)	U = 261.5
CDSS total		2.0 (2.1)	1.8 (2.5)	U = 298.0
GAF		71.2 (11.1)	63.6 (10.3)	U = 199.5*
Cognition[e]				
Cognition score	0 (.48)	0.64 (.64)	−0.27 (.62)	F = 16.28***
MWT IQ	28.2 (3.8)	27.7 (3.4)	23.2 (5.8)	F = 1.2***
RT fMRI task, in ms				
RT no reward	505.2 (68.2)	491.8 (81.5)	513.9 (91.0)	F = .49
RT low reward	471.2 (71.1)	447.5 (60.7)	488.0 (80.1)	F = 2.14
RT high reward	449.5 (71.3)	431.8 (59.4)	463.6 (81.3)	F = 1.19

Note: Data are presented as means and SDs. PANSS, Positive and Negative Syndrome Scale; BNSS, Brief Negative Symptom Scale; CDSS, Calgary Depression Scale for Schizophrenia; GAF, Global Assessment of Functioning; MWT IQ, Multiple Word Test Intelligence Quotient; fMRI, functional magnetic resonance imaging; FEP, first-episode non-affective psychosis; HC, healthy control; RT, response time; SPT, schizotypal personality traits.
[a]Diagnosis: SZ= Schizophrenia, BPD = Brief Psychotic Disorder.
[b]Apathy = Avolition, Anhedonia, Asociality.
[c]Diminished Expression = Affective Flattening or Blunting, Alogia.
[d]PANSS positive factor = P1, P3, P5, G9.
[e]Cognition data were z-transformed based on the data of the HC group for each test separately. The Composite cognition score was computed as the mean of the z-transformed test scores on subject level. Duration of illness included the duration of untreated psychosis and the time period since initiation of treatment.
*P < .05, **P < .01, ***P < .001.

been secondary due to positive and depressive symptoms. In contrast, diminished expression was not correlated with positive symptoms (r_s = −.22, P = .12) or depressive symptoms (r_s = .07, P = .63). Furthermore, there was no significant correlation between antipsychotic medication and negative symptoms in FEP patients (supplementary table S3).

fMRI Data: VS Activation During Reward Anticipation in All Groups

A voxel-wise whole-brain analysis of the reward anticipation contrast (high-reward anticipation vs no-reward anticipation) revealed strong task-related activation in reward coding regions including the VS (supplementary table S2).

To address aim 1 of the study (relation of group membership to VS activity) we compared mean contrast signal from our a priori defined VS ROI between groups (figures 3A and 3B). We did not observe any group differences between HC, FEP patients, and SPT participants in the left VS (F(2, 74) = 0.28, P = .75) and right VS (F(2, 74) = 0.07, P = .93) (figure 3C). Importantly, results did not change when controlling for age and cognition as potential confounding variables. Thus, the VS showed increased activity related to reward anticipation irrespective of group membership.

fMRI Data: Group Differences of VS Activation During Reward Anticipation Within the Psychosis Continuum

In a second group analysis we compared right VS activation during reward anticipation within the psychosis spectrum. To investigate potential different underlying neural mechanisms we defined 3 separate subgroups: individuals with high SPT, patients with brief psychotic disorders (FEP-BPD) and patients with FEP-SZ. We observed significant group differences in the right VS during reward anticipation (F(2, 46) = 4.23, P = .02, adjusted P = .04). Post hoc tests revealed increased VS activity in FEP-SZ compared to FEP-BPD (P = .04, adjusted P = .08) and SPT (P = .008, adjusted P = .016). A post hoc analysis including the high-reward and no-reward conditions separately suggested that these effects were mainly driven by relatively stronger activity during anticipation of high

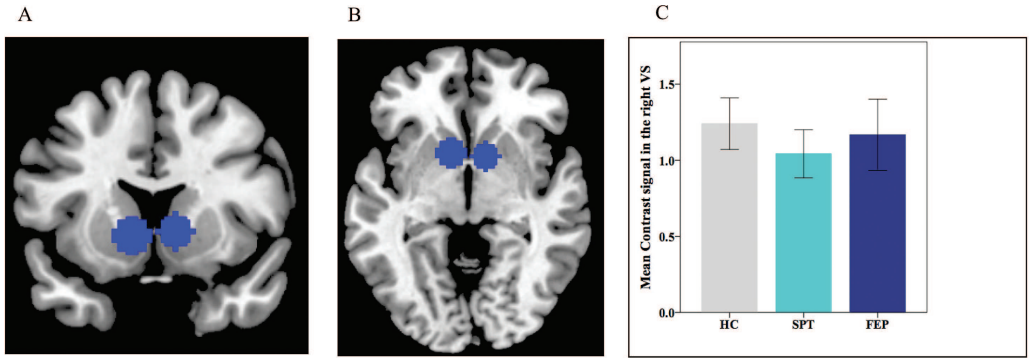

Fig. 3. (A) and (B) illustrate the ventral striatum (VS) region of interest (ROI) from which the mean contrast signal for the contrast anticipation of high reward vs no reward was extracted. (C) Columns in bar graphs reflect mean contrast signal for reward anticipation in the right VS, separately for each group. Error bars depict ± 1 SEM.

reward (supplementary figure S3). In contrast, there were no significant differences between FEP-BPD and SPT (P = .40). In the left VS no significant group differences were observed (F(2, 46) = 2.07, P = .14). In sum, these findings provide evidence that right VS activity during reward anticipation differs between FEP-SZ and other subgroups within the psychosis continuum.

Association of VS Activity With Apathy and Positive Symptoms Across the Psychosis Continuum

To address aim 2 of the study (relation of symptoms to VS activity), we calculated correlations between VS mean percent signal change and symptom dimensions across the complete psychosis continuum (FEP patients and SPT participants). Importantly, right VS activity during reward anticipation was positively correlated with apathy (r_s = .31, P = .02, adjusted P = .04), positive symptoms (r_s = .37, P = .007, adjusted P = .014) and total symptom severity (r_s = .39, P = .004, adjusted P = .008) (figure 4). Left VS activity was positively correlated with positive symptoms (r_s = .29, P = .03, adjusted P = .06) but not with apathy (r_s = .19, P = .18, adjusted P = .36) and total symptom severity (r_s = .18, P = .21, adjusted P = .42).

In contrast, diminished expression (right VS: r_s = .07, P = .60, adjusted P = 1.2); left VS: r_s = −.19, P = .17, adjusted P = .34), depressive symptoms (right VS: r_s = .22, P = .10, adjusted P = .20; left VS: r_s = .11, P = .48, adjusted P = .96), and cognition (right VS: r_s = .10, P = .48, adjusted P = .96; left VS: r_s = .24, P = .09, adjusted P = .18) were not significantly correlated with the neural signal in the VS. In summary, VS activity, in particular right VS activity, was correlated with total symptom severity, apathy, and positive symptoms.

Due to the symptom overlap of apathy, positive symptoms and depressive symptoms in our sample we computed partial correlations to identify interaction effects between these variables. Importantly, the partial correlation between VS activity and positive symptoms remained significant in the right VS (r_s = .29, P = .04), when controlling for apathy and depressive symptoms. In contrast the partial correlation between activation in the right VS and apathy was not significant (r_s = .20, P = .17) when controlling for positive symptoms and depressive symptoms. Furthermore, ventral striatal activity was not associated with antipsychotic dose in medicated patients (supplementary table S3). Finally, the inclusion of cognition and age in the partial correlations did not change the results and all correlations mentioned above remained significant (supplementary table S4).

Correlation Analysis Within Each Subgroup of the Psychosis Continuum

In a third step, we aimed to investigate if the observed relation between right VS activity and symptom expression differs between subgroups of the psychosis continuum. Therefore, we performed correlation analysis in SPT, FEP-BPD, and FEP-SZ separately (supplementary table S5). FEP-SZ showed a significant correlation between PANSS Total score and right VS activity (r_s = .60, P = .03). Furthermore, in these patients VS activity was correlated with positive symptoms at a trend level in the right VS (r_s = .50, P = .08). FEP-BPD showed significant correlation between PANSS Total score and right VS activity (r_s = .65 P = .02). Furthermore, positive symptoms were significantly associated with VS activity (right VS: r_s = .65, P = .02). In SPT, PANSS Total score was not significantly correlated with VS activity (right VS: r_s = .17, P = .42). However, positive symptoms were correlated with right VS activity at a trend level (right VS: r_s = .33, P = .10).

Since positive symptoms were consistently associated with ventral striatal activation, we repeated the ANCOVA comparing the groups within the psychosis continuum and added positive symptoms as an additional covariate. The main effect of group remained significant (F(2, 45) = 3.29, P = .046) indicating that the observed group differences cannot be reduced to differences in positive symptom levels.

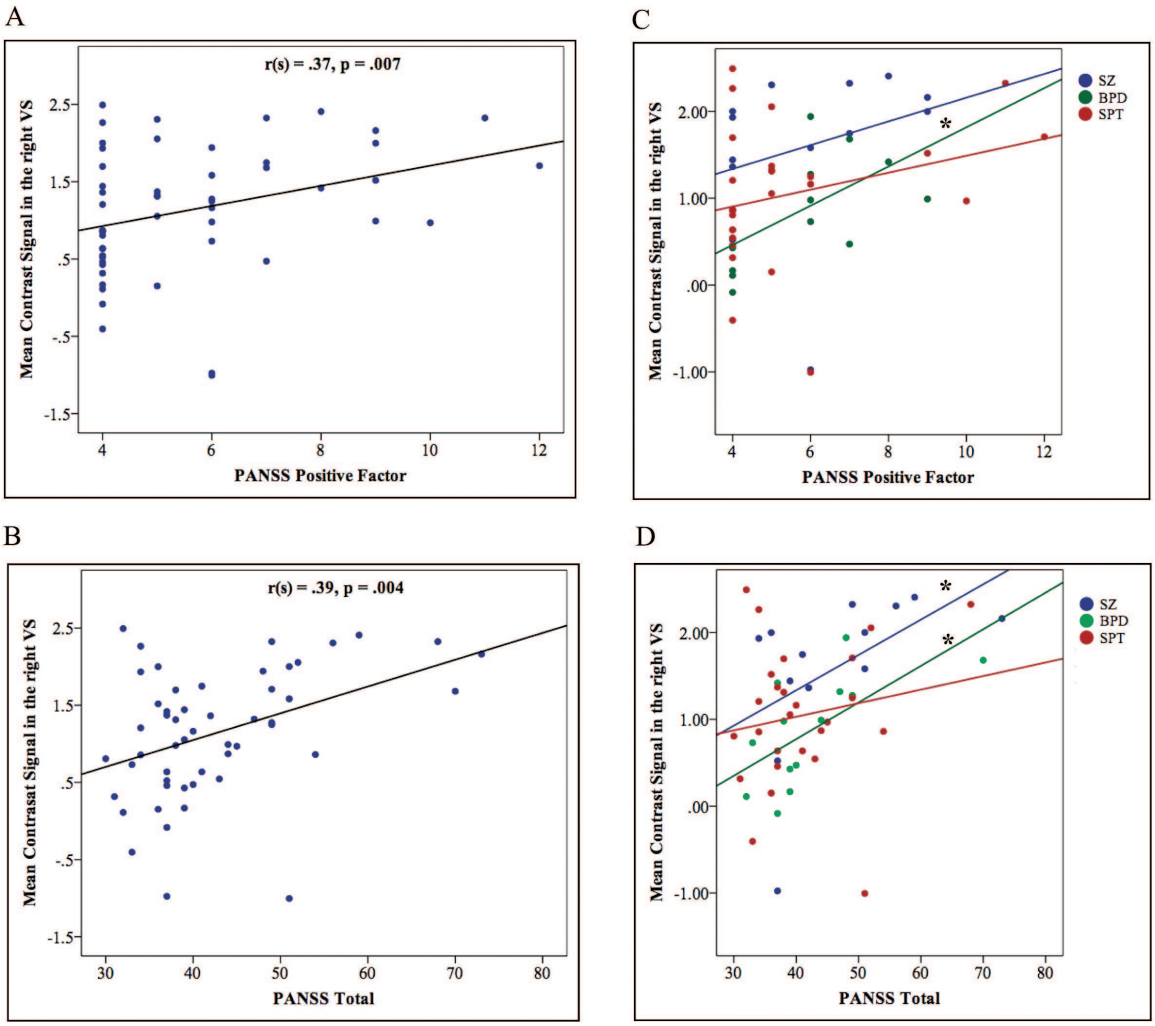

Fig. 4. Correlation plots for Positive and Negative Syndrome Scale (PANSS) positive factor (A) and PANSS total score (B) with mean contrast signal in the right ventral striatum (VS) across the psychosis continuum. Correlation plots for PANSS positive factor (C) and PANSS total score (D) with mean contrast signal in the right VS for each group within the psychosis continuum separately; first-episode schizophrenia (FEP-SZ) (n = 13), patients with brief psychotic disorders (FEP-BPD) (n = 13), and schizotypal personality traits (SPT) (n = 26). Correlation between VS activation and PANSS Positive Factor in FEP-SZ: Spearman correlation (r_s) = .50, P = .082, in FEP-BPD: r_s = .65, P = .016, and in SPT: r_s = .33, P = .101. Correlation between VS activation and PANSS Total Score in FEP-SZ: r_s = .60, P = .029, in FEP-BPD: r_s = .65, P = .016, and in SPT: r_s = .02, P = .923. * Indicates significant correlations.

Discussion

To our knowledge, this is the first functional neuroimaging study to investigate the neural correlates of symptom expression in healthy individuals with high schizotypal traits and patients with broadly defined non-affective first-episode psychosis of short duration. We observed intact reward-related speeding and no group differences, which suggests that individuals in the psychosis continuum were able to perform the task in a comparable way to HCs. We found that ventral striatal activation during reward anticipation did not differ between HCs and individuals within the psychosis continuum. In contrast, individuals with FEP-SZ showed higher VS activity compared to patients with brief psychotic disorders and individuals with high SPT.

Across these groups in the psychosis continuum, total symptom severity was associated with an increase in VS activity during reward anticipation. In particular, levels of positive symptoms were positively correlated with VS activation. In contrast, there was no association with depressive symptoms and the association with apathy was driven by positive symptoms. Importantly, the association between positive symptoms and VS activity remained when investigating each group separately.

Overall, these findings suggest that increased VS activity during reward anticipation is a shared neural correlate of positive symptoms across the psychosis continuum. However, the observed group differences point towards an increase in VS activity that is specific to FEP-SZ and cannot be reduced to symptom differences between groups.

The association of both positive symptoms and apathy with neural alterations in the VS has to be interpreted in light of the observed interaction of these symptom domains at the psychopathological level. The observed correlations suggest that in our sample apathy was at least partially secondary to positive symptoms and depression. In contrast, negative symptoms were not correlated with antipsychotics (supplementary table S3). Secondary negative symptoms are thought to result from other factors such as positive symptoms, depression and antipsychotics, while primary negative symptoms are linked to the disease process itself.[50–52] Corresponding to our findings, a specific association of apathy but not diminished expression with positive symptoms and depression has been proposed previously.[53]

At the neural level, the observed positive correlation of apathy and increased VS activity contrasts with previous studies, including our own, reporting a negative association in patients with schizophrenia.[25,26,35] However, the studies showing an association of striatal hypoactivation and apathy were typically based on samples with more primary negative symptoms in patients with chronic schizophrenia.[25,26] In contrast, the current study investigated a psychosis continuum from nonclinical participants to patients with early psychosis with a different psychopathological construct of apathy (partly secondary to positive and depressive symptoms). Furthermore, our results are consistent with findings of Morris and colleagues[54] who found the same relationship of exaggerated VS activity with negative symptoms and total symptom severity suggesting a more complex picture between aberrant ventral striatal activity and psychopathology.

Several aspects may explain the findings regarding VS hyperactivity in the present study. First, striatal responsivity to rewarding cues may be stage-dependent and vary between initial and chronic forms of psychosis resulting in relative hyper-activation in early psychosis and hypoactivation in chronic schizophrenia. Second, according to Heinz and Schlagenhauf acute psychotic symptom levels may influence reward dependent dopamine firing.[55] In acute schizophrenic psychosis chaotic aberrant firing can lead to a ceiling effect for dopamine signaling, in which signal increase related to reward cues is no longer detectable. However, in patients with low to moderate positive psychotic symptoms this ceiling effect may not be reached and signal increase related to reward cues is still detectable. Third, our data suggest that different psychopathological properties of the study samples may influence striatal function during reward anticipation. In this context, the present findings highlight the importance of differentiating psychopathological constructs when investigating the neurobiological underpinnings of symptoms and suggest different neural mechanisms for primary and secondary negative symptoms.

One of the main findings of the present study is the dimensional association of total symptom severity with VS dysfunction in the psychosis continuum. Importantly, increased striatal activity during reward anticipation was mostly driven by positive symptoms, which is consistent with our previous study in unmedicated individuals at-risk for psychosis.[19] These findings are in line with studies showing a relation between positive symptoms and increased hemodynamic responses to reward-predicting cues[56] or neutral stimuli in the mesolimbic reward system[21,32,57,58] in individuals at-risk for psychosis and patients with psychotic disorders. In contrast, a recent study in unmedicated patients with schizophrenia has reported a negative association between VS activity during anticipation of wins and losses, ie, salience, with positive symptoms.[15] The different results could be due to the fact that our study design included only reward conditions, while Nielsen and colleagues employed a salience contrast.[59,60] In addition, our patients were treated with atypical antipsychotics. However, in our subsample of medicated patients the dose of atypical antipsychotics was not associated with ventral striatal activation. Furthermore, our observation of an association between increased striatal activity with total symptom severity is in line with previous findings of elevated striatal dopamine function in positron emission tomography studies,[1,2,4,5,61,62] as well as increased striatal response in fMRI studies.[19,54]

At the group level, we found no differences between HCs and individuals with SPT or first-episode psychosis in VS activation, which is consistent with previous results in broadly defined FEP patients and individuals at-risk for psychosis.[19–22] In contrast, there is now meta-analytic support for reduced VS activation in patients with established schizophrenia,[24] but results on the individual study level are very inconsistent.[15,16,23,25,31,35,60,63,64] These mixed findings support the notion that striatal alterations in psychosis do not solely consist of hypo-activation but vary between different stages (early vs chronic) and different forms of psychosis (schizophrenia vs non-schizophrenia). In line with this notion, patients with FEP-SZ showed higher striatal activity compared to other individuals within the psychosis continuum. This effect cannot be explained by differences in symptom severity between groups. Thus, VS activation seems to be elevated in this group in addition to its relation with positive symptoms. While a mechanistic interpretation of this observation is somewhat speculative, this effect might indicate a more profound dysregulation of striatal dopamine transmission in patients with schizophrenia, possibly due to extrastriatal influences.

Some limitations of our study need to be considered. First, our sample showed only mild levels of positive symptoms and low levels of depressive symptoms, which did not differ between patients and individuals with SPT. This limits the possibility to draw conclusion about the interacting effects of the different psychopathological domains and neural correlates for high levels of symptom

expression. Thus, it would be important to investigate samples with a broader range of symptom expression on all psychosis dimensions. Furthermore, the PANSS has limitations in detecting subclinical psychotic symptoms. Future studies should focus on subclinical psychotic symptoms in at-risk groups and HCs to cover the full range of the psychosis spectrum using other rating scales such as the Comprehensive Assessment of At-Risk Mental States (CAARMS) or the Structured Interview for Prodromal Syndromes (SIPS).[65,66] In addition, the relationship between salience, value and reward prediction signals is still a matter of intense debate.[3,54,67] However, our task design focused only on reward anticipation. It would be of high importance to employ tasks that allow a clear quantitative distinction between salience and value coding in order to specify the neural basis of negative and positive symptoms. Finally, although all analyses were controlled for cognition, potential influences of differences in intelligence between groups cannot be definitely ruled out.

In conclusion, the present study provides new evidence for striatal dysfunction during reward anticipation as a dimensional neural correlate of symptom expression in the psychosis continuum. Importantly, our data suggest that increased striatal activity is associated with positive symptoms across individuals with SPT and early stages of psychosis. In line with the Research Domain Criteria approach,[68,69] these results suggest that variance in striatal activation is explained by dimensional symptom expression. However, patients with FEP-SZ show an elevated striatal activation during reward anticipation that cannot be reduced to symptom effects, which suggests an additional categorical effect separating this group from others within the psychosis continuum. These results are in line with the epidemiological literature that increasingly emphasizes combination of dimensional and categorical models of psychiatric illness.[70] Thus, our data shows that a trans-diagnostic approach facilitates disentangling dimensional and categorical neural mechanisms in the psychosis continuum.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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